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Christine Todd Whitman, Administrator
U.S. Environmental Protection Agency
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PETA
PEOPLE FOR THE ETHICAL TREATMENT OF ANIMALS

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Re: Comments on the HPV Test Plan for meta-tetramethylxylene diisocyanate

Dear Administrator Whitman:

The following are comments on the Test Plan prepared by Cytec Industries, Inc., for the compound meta-tetramethylxylene diisocyanate (TMXDI), also known as isocyanic acid m-phenylenediiso-propylidene and 1,3-bis (1-isocyanato-1-methylethyl) benzene (CAS no. 2778-42-9). These comments are submitted on behalf of People for the Ethical Treatment of Animals (PETA), the Physicians Committee for Responsible Medicine, the Humane Society of the United States, the Doris Day Animal League, and Earth Island Institute. These animal, health, and environmental protection organizations have a combined membership of more than ten million Americans.

In order to facilitate comprehension and evaluation of the Test Plan, we present here some further information on the use of, and human exposure, to TMXDI. TMXDI is manufactured by Cytec Industries, Inc. It is not marketed directly to consumers, but is reacted with a number of polyols and polyesters to make polyurethanes and other polymers. These polymers have a wide range of uses. Some are used in the manufacture of foams, but the most important uses are as coatings (e.g. paints, sealants, adhesives and lacquers) that are glossy and resistant to chemicals, weather, and mechanical damage. These coatings are used in the automobile industry (SAIC 1997), and other engineering fields. Many polyurethanes can be applied in the form of aqueous suspensions, obviating the need for organic solvents, and this property has led to an increase in their use in the US automobile industry since 1990, in order to meet the requirements of the Clean Air Act Amendments and other legislation mandating a decrease in the quantities of volatile organic compounds in automobile and other coatings (Tamaki 1997, SAIC, pp. 3-6). The polymers are also used as herbicide coatings, and as lacquers, etc., in various other fields (Data Summary and Test Plan, p. 6). In 1996 a range of polymers prepared from TMXDI was approved by the FDA for use in packaging (e.g. sealants) in direct contact with food (21 CFR Part 175).

On the whole, Cytec has done a thorough job in preparation of the Robust Summary and the Data Summary and Test Plan for the HPV Challenge Program. Cytec has recognized that most relevant toxicological data on TMXDI are already available, and are acceptable. Cytec also accepts that, for chromosomal aberration, one of the two areas for which no data are available, *in vitro* tests are superior to animal tests. However, this leaves one

additional area—developmental toxicity—for which no SIDS data were identified. On the basis of the OECD Guidelines, the smallest possible study required to satisfy the developmental toxicity requirement is a combined repeat-dose/reproductive/ developmental toxicity study, which will kill at least 675 animals (OECD Guideline 422). It is our understanding, per our discussion with Cytec on January 13, that it is this study that will be carried out, although this is not specified in the Test Plan. If the full developmental toxicity study were carried out it would kill at least 1,300 animals (OECD Guideline 414).

Cytec states that no data on the SIDS developmental toxicity endpoints for TMXDI are currently available (Robust Summary, p. 53). This may be correct since, although two animal studies (Bio-Dynamics 1987, 1992) and one human occupational exposure study (Grammer 1993) have been carried out in addition to those referred to in Cytec's documents, we also have been unable to locate developmental toxicity data.

However, the probable absence of developmental toxicity data does not *per se* present a case for carrying out additional animal experiments. First of all, note should be made of the fact that one committee of experts has made the following emphatic statement with respect to all diisocyanates: "Reproductive and developmental toxicity are not sensitive endpoints" (SAIC, p. 13).

Secondly, animal experiments are notoriously unreliable for predicting human toxicity. Developmental toxicity tests have not been validated for humans, and false-negative results would be dangerous, having the potential to encourage a spurious sense of safety. Toxicity often shows wide interspecies variability and, in the case of TMXDI, in a 14-week inhalation toxicity study, toxicity was much higher in mice (80% mortality in the highest dose group) than in rats (Cytec, Robust Summary, pp. 41-43), despite these both being rodent species. No attempt has been made to account for this wide interspecies variability. We therefore suggest that *in vitro* studies be used instead of animal studies. An *in vitro* embryotoxicity test method, the rodent embryonic stem cell test (EST), has in fact recently been validated by the European Centre for the Validation of Alternative Methods, and the Centre's Scientific Advisory Committee has concluded that this test is ready to be considered for regulatory purposes (Genschow 2002). We therefore urge Cytec to consider the use of this *in vitro* test. For additional information, please refer to Genschow's report. If a positive result is found in the EST, TMXDI should be treated as a developmental toxicant/teratogen, and no further testing should then be carried out within the *screening-level* HPV program. Although we have written to the EPA repeatedly concerning the inclusion of the EST in the HPV Program, with correspondence dating back more than six months, we have received no reply. We urge Cytec to correspond directly with the EPA on the incorporation of this validated non-animal test.

In addition, we offer the following comments on this Test Plan:

1. Occupational exposure and epidemiology studies are needed

Little relevant information is available about occupational exposure to TMXDI. On searching the databases, we found that one study has been reported on the possible effects of TMXDI and another isocyanate on the health of 96 factory workers exposed to one or both compounds (Grammer 1993). The workers were classified according to estimated levels of exposure, in order to assess the correlation between exposure and the possible effects of the compounds, but assessment of the level of exposure was not the main focus of this study.

Workers are routinely exposed to TMXDI in the process of manufacturing its polymers. Cytec maintains that exposure is by skin contact, and makes the following statements about other possible modes of exposure: "Inhalation exposure is extremely low due to the use of ventilation and the material's low vapor pressure"; "Ingestion would not be expected" (Data Summary and Test Plan, p. 5). However, no data supporting these statements are presented. In particular, it is possible that workers eat or wipe their mouths without washing their hands after handling the material. In short, it is difficult to discuss TMXDI toxicity *meaningfully* until detailed exposure and epidemiological studies have been carried out on occupationally exposed populations.

2. Reduction of occupational exposure would be beneficial regardless of whether TMXDI shows developmental toxicity

Grammer *et al*. investigated the health effects of TMXDI on workers exposed to this compound. They found no evidence for immunologically induced disease or the presence of anti-TMXDI IgG and IgE antibodies. However, they did find that 40% of exposed workers reported ocular and/or upper-respiratory irritation (1993). This suggests that insufficient attention is being given to the reduction of occupational exposure. As almost no relevant data are available, one cannot rule out the possibility that the minimum level of TMXDI exposure causing ocular and respiratory irritation is below that at which developmental toxicity can reasonably be considered possible. Consideration should therefore be given to prioritizing the reduction of exposure rather than evaluation of developmental toxicity, or, in lieu of animal testing, the EST as discussed above could be conducted as a screening mechanism.

3. Data are needed on the TMXDI monomer content of polymers

It would be helpful if Cytec's statement that "residual levels [of TMXDI monomer] are low in finished consumer products" (Data Summary and Test Plan, p. 5) were supported by quantitative chemical analysis. Unless such data are available it is impossible to estimate TMXDI exposure from consumer products.

The following statement of Cytec's is somewhat unclear:

> "In customer applications, this material is used at plants by trained personnel well equipped to handle these materials safely." (Data Summary and Test Plan, p. 5)

If this refers to applications of the TMXDI monomer, it is necessary to explain what these applications are, and how the personnel are trained and equipped. These applications should be considered in the same light as exposure to TMXDI during the manufacturing process.

If, on the other hand, Cytec's statement refers to applications for TMXDI polymers, an explanation is needed as to why the workers need to be trained and equipped for safe handling, as Cytec's position is that the polymers are almost completely safe (Data Summary and Test Plan, pp. 5-6).

Given the information presented above and the fact that reducing exposures *to humans* is more important than developing new toxicity data on the developmental effects of TMXDI *on rodents*, it is worth reiterating several provisions of the October 1999 agreement to reduce the number of animals killed in this program, namely that:

(1) In analyzing the adequacy of existing data, participants shall conduct a thoughtful, qualitative analysis rather than use a rote checklist approach. Participants may conclude that there is sufficient data, given the totality of what is known about a chemical, including human experience, that *certain endpoints need not be tested.*

(2) …As with all chemicals, before generating new information, participants should further consider whether any additional information obtained would be *useful or relevant*.

Thank you for your attention to these comments. I can be reached at 757-622-7382, ext.1304, or via e-mail at JessicaS@PETA.org.

Yours sincerely,

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